

U.S. Patent No. 10/551,475
Appendix A

Claims (Presented in February 17, 2009 Amendment)	Support in Present Application ¹	Support in Priority UK Application (UK patent 0307559.5)
<p>47. (currently amended). Library comprising a plurality of tagged ligands of formula I</p> $(LigJ_L)_m L (J_T Tag)_n (J_T L (J_L Lig)_n)_p$ <p>and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p> <p>comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L</p> <p>wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;</p> <p>L</p> <p>is selected from a <u>single</u> or double bond, -O-, -S-, amine, COO-, amide, -NNH- hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched</p>	[0014] [0173] [0014] [0045]	

¹ Support for present application is shown by citations to paragraph numbers in U.S. Publication No. 2006/0122045 A1

<p>or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinafore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;</p> <p>Tag is any tagging substrate;</p> <p>m are each independently selected from a whole number integer from 1 to 3;</p> <p>p is 0 to 3</p> <p>wherein one or more of each -Tag in one or more of each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula</p> I^p $(LigJ_r)_m L (J_r Fl)_m (J_r L (LJ_r Lig)_p)$ <p>characterised in that linking is at same or different linking sites in compounds comprising different Lig, J_r, L, J_r and/or -Tag and is at different linking sites in compounds comprising same Lig, J_r, L, J_r and/or -Tag</p> <p>wherein the or each Fl is selected from a red, near ir or blue dye with the proviso that when Lig is C₁₂H₂₄- and L is 1,1,4,4-tetramethyl- butylamine—C(CH₃)₂(CH₂)₂C(CH₃)₂NH, Fl is not BODIPY®-Fl, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NHCSNH— then Fl is not FITC, eosin or erythrosin.</p>	<p>[0015]</p> <p>[0016]</p> <p>[0017]</p> <p>[0018]</p> <p>[0027]</p>
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<p>48. (withdrawn and currently amended) Library comprising a plurality of tagged ligands of formula I</p>	<p>[0014]</p>	
<p>$(LigJ_L)_m L (J_T Tag)_n (J_T L (J_L Lig)_m)_p$</p> <p>and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p> <p>comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_L</p> <p>wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter,</p> <p>L is selected from a <u>single or double</u> bond, -O-, -S-, amine, COO-, amide, -NNH- hydrazine; and saturated or unsaturated, substituted or unsubstituted C_{1-600} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C_{1-20} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and</p>	<p>[0173]</p>	<p>[0014]</p>

	combinations thereof, and L ₁ may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 50 up to 300; is any tagging substrate;	[0015]	
Tag		[0016]	
m	are each independently selected from a whole number integer from 1 to 3;	[0017]	
p	is 0 to 3.	[0018]	
	wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which are of formula I ^p	[0027]	
	(LigJ ₁) _m L (J ₁ Fl) _m (J ₁ L (J ₁ Lig ₁) _m) _p		
	characterised in that linking is at same or different linking sites in compounds comprising different Lig ₁ , L ₁ and/or - Tag and is at different linking sites in compounds comprising same Lig ₁ , L ₁ and/or - Tag.	[0018]	
	wherein the or each Fl is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EVOBlue and fluorescent derivatives thereof, pyrenes and pyridyl/oxazole derivatives, the cyanine dyes, the dymomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the AlexaFluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycoobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.	[0015]	
49	(withdrawn and currently amended). Library as claimed in any of Claim 47 wherein each	[0028]	

<p>compound of formula I or I' comprises one of a plurality of fluorophores and/or tags providing a library of differently fluorescently tagged ligands comprising one or a number of different fluorophores optionally of different chemical composition or spectral characteristics; and/or providing a library of differently tagged ligands including at least one fluorescently tagged ligand; [0030] alternatively each compound of formula I or I' comprises one of a plurality of precursor ligands linked each to one or a plurality of different tags providing a library of same or differently tagged ligands of plural ligand type; alternatively each compound of formula I comprises one of a plurality of linkers linking a precursor ligand and at least one Tag at the same or different linking site; alternatively each compound of formula I or I' comprises the same linker linking a precursor ligand and at least one Tag at different linking sites providing a library of differently linked tagged ligands of different conformation or anticipated pharmacology and binding.</p> <p>50 (withdrawn). Library as claimed in Claim 47 comprising a plurality of compounds of one or more of formula II to III:</p> <p>II $(\text{LigJ}_L)_m L J_T \text{Tag}_T L (J_L \text{Lig})_n$ where each m is as hereinbefore defined and is preferably 1 or 2, more preferably 1</p> <p>III $(\text{LigJ}_L)_m L (J_T \text{Tag})_n$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2, more preferably</p> <p>$\text{LigJ}_L - L - J_T \text{Tag}$ and/or</p> <p>$\text{LigJ}_L - L - J_T \text{Tag}$ and/or</p> <p>$\text{LigJ}_L - L - J_T \text{Tag}$</p>	[0030]	
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J _L Lig	J _T Tag
wherein each J _L and J _T comprises J as hereinbefore defined and may be same or different and may derive from functionality originally present in Lig or L and Tag or L or a combination thereof, characterised in that linking is at same or different linking sites in compounds comprising different Lig, J _L , L, J _T and/or Tag, and is at different linking sites in the case of any two or more compounds comprising identical Lig, J _L , L, J _T and/or Tag.	
51 (withdrawn). Library as claimed in Claim 47 including information for each compound of formula I comprised in the Library, relating to the pharmacology for binding to or inhibition of a GPCR receptor or to inhibition of an intracellular cyclic nucleotide phosphodiesterase, or inhibition of or transport by a drug transporter including designation as agonist, antagonist, substrate or inhibitor and measure of affinity or inhibition, enabling quantification of results.	[0036; lines7-14]
52 (withdrawn). Library as claimed in Claim 47 wherein a GPCR ligand is selected from any compound which is effective as an agonist or antagonist for an adenosine receptor, a beta-adrenoceptor, a muscarinic receptor, a histamine receptor, an opiate receptor, a cannabinoid receptor, a chemokine receptor, an alpha-adrenoceptor, a GABA receptor, a prostaglandin receptor, a 5-HT (serotonin) receptor, an excitatory aminoacid receptor (glutamate), a dopamine receptor, a protease-activating receptor, a neurokinin receptor, an angiotensin receptor, an oxytocin receptor, a	[0021]

<p>leukotriene receptor, a nucleotide receptor (purines and pyrimidines), a calcium-sensing receptor, a thyroid-stimulating hormone receptor, a neurotensin receptor, a vasoressin receptor, an olfactory receptor, a nucleobase receptor (adenosine), a lysophosphatidic acid receptor, a sphingolipid receptor, a tyrosine receptor (trace amines), a free-fatty acid receptor and a cyclic nucleotide receptor; an inhibitor of intracellular enzymes is an inhibitor of cyclic nucleotide phosphodiesterases; and a substrate or inhibitor of a drug transporter is selected from a substrate or inhibitor of an equilibrium based drug transporter or ATP driven pump selected from a catecholamine transporter, a nucleoside transporter, an ATP-binding cassette transporter, a cyclic nucleotide transporter or derivatives or analogues thereof;</p> <p>or wherein Lig is selected from</p> <p>a) xanthine like structures including XAC, theophylline, caffeine, theobromine, dypheilline, enprofylline; or fused biaryl structures including papaverine, dihydroquinolines, cilostamide, dipyridamole or vinpocetine; and analogues thereof;</p> <p>b) adenosine like structures including ADAC, NECA and analogues thereof;</p> <p>c) ethanalamine like structures including salmeterol, salbutamol, terbutaline, quinprenalin, labetalol, sohalol, bambuterol, fenoterol, reprotohol, tulbuterol, clenbuterol and analogues thereof;</p> <p>d) oxypropanolamine like structures including CGP12177, propranolol, practolol, acebutalol, betaxolol, ICI 118551, alprenolol, celiptolol (celeclof), metoprolol (betaoloc), CGP20712A, atenolol, bisoprolol, misaprolol, carvedilol, bucindolol, esmolol, nadolol, nebivolol, oxprenolol, xamoterol, pindolol, timolol and analogues thereof;</p> <p>e) xanthine like structures including XAC, theophylline, caffeine, theobromine, dypheilline,</p>	<p>[0038]</p> <p>[0039]</p> <p>[0022]</p> <p>[0023; 1ines 9-13]</p> <p>[0040]</p>
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enprofylline, sildenafil, EHNA (erythro-9-(2-hydroxy-3-nonyl)adenine), zaprinast; or spiro bicyclic structures including bypyridines, amrinone; imidazolines, C1930; dihydropyridazinones, indolan, rolipram, SB207499; or fused biaryl structures including papaverine, dihydroquinolones, cilostamide, dipyridamole, vincocetine and analogues thereof.	[0041]	
53 (withdrawn). Library as claimed in Claim 47 wherein J_{1m} L J_{1m} comprises a mono, di, tri, tetra, penta, or hexa amino, alkylthio, alkoxy, carboxylic acid, and combinations thereof including a mono, di or tri aminoalkylthio, amino alkoxy, alkoxy carboxylic acid or alkoxy amine, mono, di or tri amino menthane, amino ethane, thio ethane, ethane, amino acyl, polypeptide, or mono or polyether derivatives including diamine or dithio derivatives, mono or polyethylene glycol di or tri amine or thio; or comprises a mono-, di-, tri- or tetra, penta or hexafunctional linear or branched or cyclic substituted or unsubstituted hydrocarbyl of formula $-L_1-$	[0049]	[0050]

$J [A] q_L [A' q_L' J']_p A'' q_L'' J''$

wherein each of J to J'' is a linking site or functionality as hereinbefore defined independently selected from a single or double bond, methylene, alkyne, alkene, NR, O, CONR, NRCO, S, CO, NCO, CHHal and P wherein R is H or C_{1-8} alkyl or cycloalkyl or forms part of a cyclic ring with N, Hal is any halogen selected from chlorine, iodine, bromine; and is present in any rational

<p>location in a group A to A'', each of A to A'', is a group selected from $-O-$, $-C(=O)-$, C_{1-2} alkoxy, alkoyl, cycloalkyl, heterocyclic, alkyl, alkenyl, aryl, arylamide, arylamine, amino, thioalkyl, heteraryl as hereinbefore defined and combinations thereof, optionally substituted by groups selected independently from C_{1-3} alkyl and C_{1-5} alkoxy;</p> <p>each of q_L to q_L'' are independently-selected from 0 or 1 or indicates an oligomeric repeat and is from 2 to 30, or indicates a polymeric repeat unit and is from 31 up to 300.</p> <p>R_L is a C, N or S atom or is a CR_L, NR_L, alkyl, cycloalkyl, heterocyclic, aryl heteroaryl, amine or thio moiety and provides for branching when p is 1 or 2; wherein R_L is H or C_{1-3} alkyl; and</p> <p>p is as hereinbefore defined and is 0, 1 or 2.</p>	<p>[0052]</p>
<p>54. (withdrawn). Library as claimed in Claim 47 wherein $J_{Ln} L J_{ln}$ is of formula $J A q_L R_L J''$ wherein each of J and J'' is amine or $-O-$, A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2 or of formula $J A q_L R_L (A' J') J''$ wherein each of J, J' and J'' independently is amine, $-O-$ or a single bond, q_L is 1, 2 or 3, 3-30 or 31 to 300 and A is CH_2CH_2O or $HNCH_2CO$ or q_L is 1 and A is $C(O)$ or $(CH_2)_{1-8}$ or q_L is 0, R_L is CH or CH_2CH, q_L is 0 or q_L' is 1 and A' is CH_2 and q_L'' is 0</p>	<p>[0059]</p> <p>[0051]</p>

preferably

O(CH₂CH₂O)qLCH₂CH₂NH, O(CH₂CH₂O)qLCH₂CH(CH₂NH)NH,
OCH(CH₂NH)NH, -CH(CH₂NH)NH, -C(O) NH, -(CH₂)₁₋₈- or (-HNCH₂CO-)₁₋₃ (= -gly₁₋₃-) -.

55. (withdrawn). Library as claimed in Claim 47 wherein each compound of formula I or I'

comprises a moiety Lig and L as hereinbelow defined:

Wherein:

any optically active fluorescent ligand is present as a racemate or as one of its optically active

isomers

Lig_{am} is suitably of the formula, in either of the following forms given, including any of its possible linking configurations or sites:



[0060]

[0061]

[0062]

Liga¹
m

Wherein

at least one or all of Ra¹ to Ra⁴, X¹ and X² comprise a linking site or functionality J as hereinbefore defined

X¹ and X² are each independently selected from H, O, OR_a, NR_a, NHR_a;

X¹ and X² are each preferably O;

each of Ra¹, Ra², Ra³ and Ra⁴ independently is selected from H or C₁₋₄ linear or branched alkyl optionally mono or multi hydroxy or halo substituted;

Ra⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo and cyano; including optionally substituted aryl, cycloalkyl, alkyl, ketone, (d)amine, (di)amide, alkoxy, cycloalkyl, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl,

[0063]
[0064]

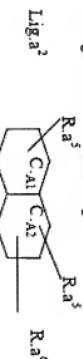
[0065]

[0066]

[0067]

alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl or R.a⁴ comprises cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)₂CONH, CH₂CONH(CH₂)₂NH, CH₂PhNHCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₂)₂NCOCH₂, H₂N(CH₂)₈NHCOCH₂, H₂NNHCOCH₂, HOPhCH₂N(CH₂CH₃)HOAc(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)₄CONH(CH₂)₂NHCOCH₂ or heterocyclic-NHCON(heterocyclic)COCH₂;

or Lig_a is of the formula Lig_a²



wherein at least one or all of R_a⁵ to R_a⁶, or a cyclic C or heteroatom comprise a linking site or functionality J as hereinbefore defined, each of C_{A1} and C_{A2} is independently selected from C₅₋₆ aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group; Each of up to seven R_a⁵ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain

[0068]
[0069]

[0070]

[0071]

aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O or cyano; OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)₂hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;

or any two or more of R.^a⁵ form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.^a² structure;

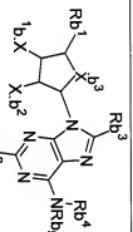
and R.^a⁶ is a moiety as defined for R.^a⁵ above;

and L.^a is as hereinbefore defined for L or J_L L_J or subformulae as hereinbefore defined, or is a single bond, amino acid or amide including a peptide or polypeptide gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, optionally including one or more heteroatoms or unsaturated groups, including -O- or -S- or -CH=CH-;

[0073]

Lig.^b is suitably of the formula Lig.^b including any of its possible linking configurations or sites:

Lig.^b



wherein at least one or all of Rb¹ to Rb⁵ or Xb¹ to Xb³ comprise a linking site or functionality J as hereinbefore defined

[0074]

ring substituents Xb¹ and Xb³ are independently selected from hydrocarbon including alkyl or SRx, NRx₂ and ORx wherein (each) Rx is selected from H, C₁₋₅alkyl, alkenyl; ring heteroatom Xb³ is selected from -S-, -O- and -CH₂-;

[0075]
[0076]

Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic,

or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; or Rb¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, cyclopropyl, or CONHC₁₋₃alkyl including CONHET or CH₂OH

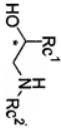
and each of Rb² and Rb³ is selected from H, halo, hydroxy, thiol, amine, COOH,

CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋

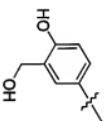
20 branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as

[0077]

[0078]

<p>hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, preferably from H, halo or hydroxy;</p>	
<p>Rb^4 is H;</p>	<p>[0079]</p>
<p>Rb^5 is H or alkyl</p>	<p>[0080]</p>
<p>L.b comprises a linking site or functionality J as hereinbefore defined; and is as hereinbefore defined for L or its subformulae, more preferably is saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for L, optionally including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, or is of formula L.I or its subformulae as hereinbefore defined, or is (CH₂)_m wherein m is 2 to 12, or is (Ph-CH₂CONHb₂ (CH₂)_b;</p>	<p>[0081] [0082]</p>
<p>Lig.c is of the formula Lig.c including any of its possible linking configurations or sites:</p>	
<p>$HOC^*(R.c^1)CH_2NH-RC^2$</p>	
<p></p>	
<p>where at least one or all of Rc¹ to Rc² or OH, or a chain C or N comprise a linking site or functionality J as hereinbefore defined</p>	<p>[0083]</p>
<p>* indicates an optically active centre and</p>	<p>[0084]</p>
<p>wherein R.c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O,</p>	<p>[0085]</p>

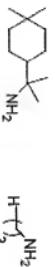
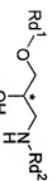
optionally substituted by OH, Hal, NH₂, NHC₁₋₃alkyl sulphonamide, oxoamine or (-CONH₂), or is mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, or is m-CH₂OH, p-OH phenyl, m,p-dihydroxy phenol or m,m-dihydroxyphenol, m,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline,



R_c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano and combinations thereof, or R_c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ aliphatic optionally substituted by OH and optionally including heteroatoms selected from N, O, optionally including an ether O, and is selected from -(CH₂)₆OCH((CH₂)₂)Ph, CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH,

[0086]

[0087]

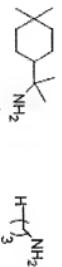


L.c

is present as R.c² or comprises a linking site or functionality J as hereinbefore defined, and is as hereinbefore defined for L, formula L.I or its subformulae as hereinbefore defined, or is selected from C₁₋₁₂ alkyl, amide;

[0088]

C(CH₃)₂CH₂Ph or from the structures:



Lig.d is of the formula Lig.d including any of its possible linking configurations or sites:

Lig.d R.d¹ OCH₂C*HOHCH₂NH-R.d²

where at least one or all of R.d¹ to R.d² or OH, a chain C or N comprise a linking site or functionality J as hereinbefore defined

* indicates an optically active centre

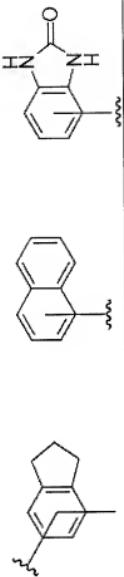
wherein R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional

[0089]

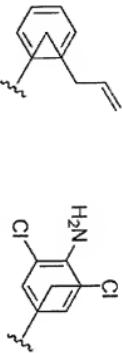
[0090]
[0091]

substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano; or R_{d1} is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo or OH, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl including phenyl, carbazole or structures shown below or spiro ring systems, mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems:

[0092]

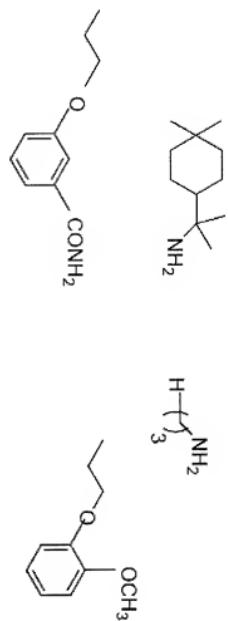


[0092]



R_{d2}

is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo or cyano, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, or of the formula:



L.d

may be present as R.d² or may comprise a linking site or functionality J as hereinbefore defined and is as hereinbefore defined for L and its subformulae, formula L.I and its subformulae as hereinbefore defined, or is a single bond or is as hereinbefore defined for L.a;

Lige comprises a cell permeant moiety or is associated with a cell permeant L or Fl moiety or is of the formula , in either of the following forms given including any of its possible linking configurations or sites:

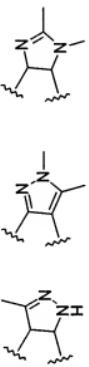
Lige¹



[0095]
[0096]

wherein

at least one or all of Re¹ to Re⁴, X and a ring C or N comprise a linking site or functionality J as hereinbefore defined
is selected from h



[0097]

each optionally substituted by R.e³ – R.e⁴ wherein R.e¹ – R.e⁴ are as R.a¹ – R.a⁴ defined above or in which R.e³ is C₅ linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy or

sulfonyl,



[0098]

ortho-OEt, meta-SO₂N
each X is independently selected from H, O, -OR^e, N, HN, NR^e, HR^e, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted or is Ph-ortho-OCH₂CH₂CH₃;

[0099]

and where R^e⁵ is as defined above for R^e¹ above or forms a fused cyclic ring together with the adjacent ring N atom, or 1 or 2 fused 5 membered cyclic rings;

[0100]

and R^e⁶ is as defined above for R^e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether, o-ethoxy or o-propoxy, alkyl or OH, sulphonyl or carbonyl substituted by heterocyclic, or cyclic C₅₋₈ alkyl, piperazinyl or sulphonyl;

or Lig^e is of the formula Lig^e²

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[0101]
[0102]

wherein at least one or all free ring atom or their substituents comprise a linking site or functionality J as hereinbefore defined each spiro ring optionally comprises zero or one or more heteroatoms h

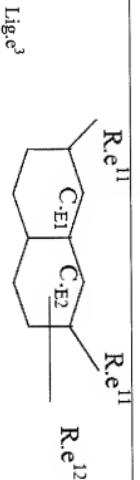
or (h) comprises zero or 1 N

[0103]

heteroatom and (h) 5,6(h) comprises zero, 1 or 2 N heteroatoms and is unsaturated or comprises one or two -C=C- or -C≡N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

[0104]

or Lig.e is of the formula Lig.e³



wherein at least one or all of $R.e^{11}$ to $R.e^{12}$, or a ring C or heteroatom or ring substituent comprise a linking site or functionality J as hereinbefore defined

[0105]

each of $C.E1$ and $C.E2$ is independently selected from C_{5-6} aryl, heteroaryl, cycloalkyl and heterocyclic, including phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring $-C=C-$ group; each of up to seven $R.e^{11}$ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo =O, or cyano, OCH_3 , $CH_2Ph(OCH_3)_2$,

[0106]

[0107]

[0108]

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<p>O(CH₂)₅CON(CH₃)₂hex, N(CH₂CH₂OH)₂, c.hex, COOCH₂CH₃, CH₂CH₃;</p> <p>or</p> <p>any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, a fused 3 ring aryl, 5-heterocyclic or 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;</p> <p>and</p> <p>R.e¹² is a moiety as defined for R.e¹¹ above;</p>	<p>[0109]</p>
<p>L.e</p> <p>comprises a linking site or functionality J as hereinbefore defined and is suitably as hereinbefore defined for L.a.</p>	<p>[0110]</p>
<p>56. Canceled</p>	<p>[0112]</p>
<p>57</p> <p>(withdrawn). Library as claimed in Claim 55 wherein F1 is of formula J_T - t - F1 and comprises a BODIPY™ structure characterised by a dipyrrometheneboron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent --t-- is adapted for linking as hereinbefore defined to a ligand precursor as hereinbefore defined, wherein the substituent --t-- comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, halacetamide or sulphonate ester</p>	<p>[0118, line 8]</p>
	<p>[0120: line 9- end]</p>

electrophilic group.

58. Canceled		
59. (withdrawn and currently amended). Process for the preparation of a library as claimed in of Claim 47 which is a combinatorial process; and comprises the reaction of one or more ligand precursors of formula IV and/or IV'	[0132]	
IV (Lig _L) _m -L-Y _{Lm}		
IV' Lig Y _{Lgm}		
comprising one or more or different reactive groups Y _L or Y _{Lg} forming a linking functionality J _L or J _T as hereinbefore defined		
with one or more of a plurality of analytical tagging substrates of formula V and/or V'		
V Y _{Tm} Tag		
V' Y _{Tm} L (J _T Tag) _m		
comprising one or more or different reactive groups Y _T forming a linking functionality J or J _T as hereinbefore defined		
and optionally one or more linking species VI or VI' or VI''		
VI Y _{Lm} -Y _{Lm}		
wherein Lig, J, L, J _T and Tag and each m is independently as hereinbefore defined		

wherein the or each compound of formula IV or IV' is capable of reaction with the or each compound of formula V or V', optionally via the or each species VI or VI' or VI'', to form a plurality of compounds of formula I as hereinbefore defined; wherein linking is at same or different reactive sites in different compounds as hereinbefore defined.

60 (withdrawn and currently amended). Process for the preparation of a compound of formula I as hereinbefore hereinbelow defined in Claim 47-64 comprising the reaction of a compound of formula IV or IV' and a compound of formula V or V' and optionally additionally VI, as hereinbefore defined in claim 59, by reacting the unprotected primary alkyl-amine group of a compound of formula IV with a compound of formula V comprising a reactive succinimidyl ester-group in solvent at ambient temperature without the need for subsequent deprotection.

[0142]

61-62 (canceled).

63 (withdrawn and currently amended). Method-Process as claimed in Claim 62 59 which comprises additionally determining pharmacology for a plurality of or all compounds in the library in order to enable selecting a compound exhibiting desired pharmacology, whereby the process comprises preparing a preliminary library of compounds, conducting screens to assess binding or

[0154, line 6-
8]

[0155]

inhibition, selecting a compound identified in the screen as having beneficial properties, and modifying or functionalising by nature of moieties or linking location of linking on the basis of the indications from the screen to prepare an optimised library, wherein the molecular pharmacology and photochemistry from the screen feedback into the design of the library.

64. (currently amended). A compound of formula I

$(\text{Lig}_1\text{J}_1)_m \text{ L} (\text{J}_1\text{-Tag})_n (\text{J}_1\text{ L} (\text{J}_1\text{ Lig})_n)_p$

or salt thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers

comprising ligand moiety Lig linked to tag moiety Tag via linker moiety L at linking site or linking functionality J₁ and J₂

wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NNH- hydrazine; and saturated or unsaturated substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore

[0159]

[0173]

[0114]

[0045]

defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300; m are each independently selected from a whole number integer from 1 to 3; p is 0 to 3

wherein -Tag is a fluorophore entity -Fl whereby the compound is of formula I'



characterised in that Fl is selected from a red, near ir or blue dye

with the proviso that:

a) when Lig is XAC ie in Lig.a when each of R_a¹ and R_a² is propyl, R_a³ is H and R_a⁴ is -Ph-

OCH₂CONH(CH₂)₂NH, and L is a single bond Fl is not BODIPY™ 630/650 X, or

b) when Lig is ABEA, ie m is 4 and L is a single bond Fl is not BODIPY™ 630/650 X, as hereinbefore defined in Claim 47 wherein L_mL-T_{4m} is of formula



wherein each of J₁ and J₂ is amine or -O-, A is -CH₂CH₂O-, q₁ is 1-30 or 31-300 and R₁ is



or of formula



wherein each of J₁, J' and J'' independently is amine, -O- or a single bond, q₁ is 1, 2 or 3-30 or 31 to 300 and A is -CH₂CH₂O- or -HNCH₂CO- or q₁ is 1 and A is -C(O)- or -(CH₂)₁₋₈ or q₁ is 0, R₁ is -CH₂CH₂ or q₁ is 0 or q₁ is 1 and A' is -CH₂ and q₁ is 0

[0015]

[0017]

[0018]

[0027]

[0115]

[0170]

[0171]

preferably
 $\text{OCH}_2\text{CH}_2\text{O}^{\text{q1}}\text{CH}_2\text{CH}_2\text{NH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O}^{\text{q1}}\text{CH}_2\text{CH}(\text{CH}_2\text{NH}_2)\text{NH}_2$,
 $\text{OCH}(\text{CH}_2\text{NH}_2\text{NH}_2\text{CH}(\text{CH}_2\text{NH}_2\text{NH}_2\text{CO})\text{NH}_2$, $-(\text{CH}_2)_3$ - or $-(\text{HNC}\text{H}_2\text{CO})_{1-3}$)- and
wherein any optically active fluorescent ligand is present as a racemate or as one of its optically
active isomers;

65. (currently amended). A compound of formula I as defined in Claim 64 which is a
compound of formula II or III as hereinbefore defined in **Claim 50**
II $(\text{LigL}_m\text{L}_1\text{J}_1\text{TagJ}_1\text{L}_1\text{J}_1\text{Lig})_m$ where each m is as hereinbefore defined and is preferably
1 or 2, more preferably 1

III $(\text{LigL}_m\text{L}_1\text{J}_1\text{Tag})_m$ wherein each m is as hereinbefore defined and is preferably 1 and/or 2,
more preferably

Lig $\text{J}_1\text{L}_1\text{L}_1\text{J}_1\text{Tag}$ and/or

Lig $\text{J}_1\text{L}_1\text{L}_1\text{J}_1\text{Tag}$ and/or Lig $\text{J}_1\text{L}_1\text{L}_1\text{J}_1\text{Tag}$

$\text{J}_1\text{L}_1\text{Lig}$

as hereinbefore defined in **Claim 50** and wherein any optically active fluorescent ligand is present
as a racemate or as one of its optically active isomers.

[0030]

<p>66. (currently amended). A compound according to Claim 64, wherein Fl is of formula $\text{I}-\text{t}-\text{Fl}$ and comprises a BODIPY™ structure characterised by a dipyrrometheneboron difluoride core, optionally modified by one or two fused rings, optionally substituted by one or several substituents selected from alkyl, alkoxy, aryl or heterocyclic, wherein one substituent $-\text{t}$ is adapted for linking as hereinbefore defined to a li and precursor as hereinbefore defined, wherein the substituent $-\text{t}$ comprises a proximal unsaturated or aryl moiety, comprising a medial short, medium or long chain alkynyl or cycloalkynyl moiety and comprising a moiety derived from linking via a reactive group as hereinbefore defined or selected from carboxyl, sulphonate or as a heteroatom O or S or methylene derived from linking at an alkylhalide including methylbromide, haloacetamide or sulphonate ester electrophilic group. Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter or Fl is a fluorophore entity, with the proviso that when Lig is CGP12177 and L is 1,1,4,4-tetramethylbutylamine $\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{NH}$, Fl is not BODIPY®-Fl, or when L is $\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2\text{NHCSNH}$ then Fl is not FHC eosin or erythrosin BODIPY®-630/650 or BODIPY®-630/650-X.</p>	<p>[0118]</p> <p>[0120; line 9- end]</p>
<p>67. (currently amended). A compound of the formula I or I' as hereinbefore defined in Claim 56 <u>55</u> selected from formulae $\text{Lig}_{\text{A}_\text{m}}\text{L}_{\text{A}'}\text{Fl}_{\text{A}_\text{m}}$ to $\text{Lig}_{\text{C}_\text{m}}\text{L}_{\text{C}'}\text{Fl}_{\text{C}_\text{m}}$ as hereinbefore defined with the proviso that:</p>	<p>[0159]</p>

a) when Lig is XAC ie in Lig-a when each of Ra¹ and Ra² is propyl, Ra³ is H and Ra⁴ is Ph—OCH₂CONH(CH₂)₂NH₂, and L is a single bond or L is gly and n=3 or L is NCS, Fl is not fluorescein; or

b) when Lig is adenosine Fl is not Fmoc (CA 134:204756); or
when Lig is ADAC, ie R_a¹ is CH₂OH, R_a² and R_a³ are H and L is (Ph—CH₂CONH)₂(CH₂)₂ or L is a single bond, Fl is not fluorescein, NBD or Rhodamine; or
when Lig is NECA (neorporating the moiety—(CH₂)₆—) ie R_a² and R_a³ are H and L is a single bond, or is (CH₂)_m when m is 2,4,6,8 or 10 then Fl is not NBD, or when m is 3,4,6,8,10 or 12 then Fl is not dansyl; or

when Lig is N⁶[2-(4-aminophenyl)ethyl]adenosine and L is (CH₂)₂PhNH, Fl is not FITC (CA 121:56155 (4))

c) when Lig is CGP12177 and L (R^a³) is mero-anime-methane, Fl is not BODIPY® TMR; or

when Lig is CGP12177 and L is 1,1,4-tetramethyl—butylamine, ie C(CH₃)₂(CH₂)₂C(CH₃)₂NH—Fl is not BODIPY® Fl, or when L is C(CH₃)₂(CH₂)₂C(CH₃)₂NC(S)NH— then Fl is not FITC, eosin or erythrosin; or when L is meroanine-methane, Fl is not FITC (CA 131:56155 (4)); or

when Lig is CGP12177 and L is a single bond, Fl is not NBD; or
when Lig is alprenolol i.e o-prop 2-etyl phenyl and L is C(CH₃)₂ or a single bond, Fl is not NBD;

and a) e) when L is a single bond, Fl is not BODIPY Fl;

<p>optionally; additionally</p> <p>a) when Lig is XAC ie in Lig a when each of R.a¹ and R.a² is propyl, R.a³ is H and R.a⁴ is -Ph-OCH₂CONH(CH₂)₂NH⁺, and L is a single bond F1 is not BODIPY™ 630/650 X; or</p> <p>b) when Lig is ABEA, ie m is 4 and L is a single bond F1 is not BODIPY™ 630/650 X.</p>	<p>[0170] [0171]</p>
<p>68. (currently amended). A compound of the formula I</p> $(LigJ)m L (J-Tag)n (J-L (J-Lig)m)b$ <p>or salt thereof and salts thereof wherein an optically active ligand is present as a racemate or as one of its optically active isomers</p> <p>comprising ligand moiety Lig linked to tag moiety Tag via linker moiety L at linking site or linking functionality J₁ and J₂ wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter</p> <p>L _____ is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN- hydrazine; and saturated or unsaturated, substituted or unsubstituted C₁₋₆₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein</p>	<p>[0159]</p> <p>[0173]</p> <p>[0114] [0045]</p>

optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric

repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300:

m _____ are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein -Tag is a fluorophore entity -Fl, whereby the compound is of formula I'

$$(L_{\text{Lig}})_m L (J_T F L_m (J_T L (J_L L_{\text{Lig}})_m)_p$$

LigJ_b-LJ_f-Fl as defined in claim 47

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active

active isomers

wherein F1 is a fluorophore as hereinbefore defined and is selected from the class of dyes in particular—including fluorescein, fluorescein derivatives including FITC, and fluorescein-labeled molecules including Oregon Green™ and its derivatives, Texas red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD)—and derivatives thereof—coumarin and derivatives, naphthalene—including derivatives of dansyl chloride or its analogues or derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridylloxazole derivatives, the cyanine dyes, the dyes (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the AlexaFluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrenes, anthracenes, acridines, fluorescent phycoobiliproteins and their conjugates and

[5110]

[0017]

[5100]

fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™, including the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol-Green™, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups, and
wherein Lig-J₅-L-J₇ is selected from:

xanthine-like structures

adenosine-like structures;

ethanolamine-like structures; and

oxypropanolamine-like structures; wherein

linking functionality L₇ is amine; and

wherein linker L is selected from branched and straight chain C₁₋₂₀alkyl, C₆₋₂₀oxyalkyl, or any and combinations thereof, optionally comprising one or more heteratoms O and optionally substituted by C₁₋₁₂aliphatic, or xanthine-like structures; L is also selected from a single bond, with the proviso that when Lig is XAC₁ in Lig a when each of R_a¹ and R_a² is propyl, R_a³ is H and R_a⁴ is -Ph-OCH₂CONH(CH₂)₂NH⁻, and L is a single bond Fl is not BODIPY™ 630/650 X, or X, or

b) when Lig is ABEA, ie n is 4 and L is a single bond Fl is not BODIPY™ 630/650 X.

[0170]

[0171]

69 (withdrawn). A kit comprising a Compound of formula I or I' as hereinbefore defined in [0157]
Claim 47 associated with information relating to its pharmacological properties in the form of
Spectral Properties given as Excitation Max and Emission Max, Fluorescence Lifetime and
Emission quantum yield and Pharmacology defined in terms of cells expressing a GPCR receptor
as hereinbefore defined or expressing an intracellular cyclic nucleotide phosphodiesterase, or a
drug transporter as hereinbefore defined and given as the Inhibition or Antagonism of receptor
binding or of receptor functionality together with a value for the Inhibition (pK_b) or Antagonism
(pK_i) binding constants, and optionally together with fluorescent images of the pharmacological
binding in single living cells illustrating the defined inhibition or antagonism, preferably the
pharmacological properties are given as EC₅₀ values for agonist stimulated – or pK_i values for
antagonism of agonist stimulated second messenger generation, or substrate K_m values or
antagonist K_i values for stimulation or inhibition of intracellular enzymes or drug transporters.

[0158, lines
17-21]

70 (currently amended). Compound of formula IV or IV' or library thereof as hereinbefore defined in Claim 59-useful-for-linking-to-any-suitable-tag-of-formula-V-or-V'-as-hereinbefore defined-in-Claim-59,

wherein the linker moiety is of formula

J-Ag₂-R_L-J'

wherein each of J and J' is amine or —O—, A is —CH₂CH₂O, q_L is 1-30 or 31 to 300 and R_L is

CH₂CH₃

or of formula

J-Ag₂-R_L(A'J')-J'

wherein each of J, J' and J'' independently is amine, —O or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A' is —CH₂CH₂O or —HNCH₂CO or q_L is 1 and A is C(O) or (CH₂)₄S or q_L is 0, R_L is —CH₂CH₂CH₃, q_L is 0 or q_L' is 1 and A' is —CH₂ and q_L'' is 0

preferably

—CH₂CH₂CH₂NH₂, —CH₂CH₂NH, —CH₂CH₂O^{q_L}, —CH₂CH₂(CH₂NH₂)NH₂,
—CH₂CH₂NH₂NH₂, —CH₂CH₂NH₂NH, —C(O)NH₂, —(CH₂)₄S or (—HNCH₂CO)₄S (=glycyl-).

[0179]

71 (withdrawn and currently amended). Fluorophore linker of formula V' or library thereof as

[0180]

<p>hereinbefore defined in Claim 59 wherein the linker moiety is of formula $J-Aq_L-R_L-J'$ wherein each of J and J' is amine or $-O$, A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2 or of formula $J-Aq_L-R_L(A^2P_J)J'$ wherein each of J, J' and J'' independently is amine, $-O$ or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is CH_2CH_2O or $HNC(=O)CO$ or q_L is 1 and A is $C(=O)$ or $(CH_2)_{1-s}$ or q_L is 0, R_L is CH_2CH_2, q_L is 0 or q_L is 1 and A^2 is CH_2 and q_L is 0 preferably OCH_2CH_2O, CH_2CH_2NH, $OCH_2CH_2Oq_LCH_2CH_2(C(=O)NH_2)NH$, $OCH_2CH_2NH_2$, $CH_2CH_2NH_2$, $C(=O)NH_2$, $(CH_2)_{1-s}$ or $(HNC(=O)CO)_{1-s}$ ($=g_1^2y_1z_1$)).</p>	<p>hereinbefore defined in Claim 59 wherein the linker moiety is of formula $J-Aq_L-R_L-J'$ wherein each of J and J' is amine or $-O$, A is CH_2CH_2O, q_L is 1-30 or 31 to 300 and R_L is CH_2CH_2 or of formula $J-Aq_L-R_L(A^2P_J)J'$ wherein each of J, J' and J'' independently is amine, $-O$ or a single bond, q_L is 1, 2 or 3-30 or 31 to 300 and A is CH_2CH_2O or $HNC(=O)CO$ or q_L is 1 and A is $C(=O)$ or $(CH_2)_{1-s}$ or q_L is 0, R_L is CH_2CH_2, q_L is 0 or q_L is 1 and A^2 is CH_2 and q_L is 0 preferably OCH_2CH_2O, CH_2CH_2NH, $OCH_2CH_2Oq_LCH_2CH_2(C(=O)NH_2)NH$, $OCH_2CH_2NH_2$, $CH_2CH_2NH_2$, $C(=O)NH_2$, $(CH_2)_{1-s}$ or $(HNC(=O)CO)_{1-s}$ ($=g_1^2y_1z_1$)).</p>
<p>72 (withdrawn and currently amended). Kit comprising ligand precursors, linker precursors and tag precursors of formulae IV, IV', V, V' and/or VI as hereinbefore defined in Claim 59 for preparing a library of compounds of formula 1 $(LigJ)_m\ L\ (J_T-Tag)_n\ (J_T\ L\ (J_T\ Lig)_m)_p$ and salts thereof wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers</p>	<p>[0181]</p>

comprising one or a plurality of same or different ligand moieties Lig each linked to one or a plurality of same or different tag moieties Tag via same or different linker moieties L and same or different linking site or linking functionality J_T and J_T wherein Lig comprises a GPCR ligand, an inhibitor of an intracellular enzyme or a substrate or inhibitor of a drug transporter;

L is selected from a single or double bond, -O-, -S-, amine, COO-, amide, -NN- hydrazine, and saturated or unsaturated, substituted or unsubstituted C₁₋₄₀₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁₋₂₀ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano and carbonyl and combinations thereof, and L may be monomeric, oligomeric having oligomeric repeat of 2 to 30 or polymeric having polymeric repeat in excess of 30 up to 300;

Tag is any tagging substrate;

m are each independently selected from a whole number integer from 1 to 3;

p is 0 to 3

wherein one or more of each -Tag in one or more or each library compound is a fluorophore entity -Fl, whereby the library comprises compounds of which one or more or all of which compounds are of formula I'

(LigJ_T)_m L (J_T Fl)_m (J_T L (J_L Lig)_m)_p

[0045]

[0015]

[0016]
[0017]

[0018]

[0027]

characterised in that wherein linking is at same or different linking sites in compounds comprising different Lig, J_L, L, J_T and/or - Tag and is at different linking sites in compounds comprising same Lig, J_L, L, J_T and/or - Tag with the proviso that when Lig is -CGB12177 and L is 1,1,4,4-tetramethyl- butylamine C(CH₃)₂(CH₂)₂C(CH₃)₂NH₂, F1 is not -BODIPY® FL, or when L is -C(CH₃)₂(CH₂)₂C(CH₃)₂NH₂ — then F1 is not FHC, eosin or erythrosin wherein the or each F1 is selected from a red, near ir or blue dye.

[0115]

73 (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof as hereinbefore defined in Claim 47 for visualising receptors or receptor binding, assessing pharmacological properties of the fluorescent ligand, in high throughput screening of novel chemical entities that bind to the target receptor, in inhibiting an

[0182, lines
1-10]

			intracellular enzyme or inhibiting a drug transporter or a substrate of a drug transporter, in studying drug transport or drugs suitable for transport or in distinguishing healthy or diseased tissue.
74	(withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof thereof as hereinbefore defined in claim 47 or 64 for use in a method for receptor binding or inhibition, intracellular enzyme inhibition or drug transport or inhibition and visualisation comprising contacting the library or a compound thereof as-defined in claim 47 with a sample comprising live cell material comprising GPCRs, intracellular enzymes or drug transporters in manner to facilitate binding or inhibition thereof or transport thereby, and detecting changes in fluorescence or location thereof.	[0183]	
75.	(withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof is a fluorescent ligand(s) which has affinity such that it binds permanently, semi-permanently or transiently and remains bound when unbound ligand is washed away.	[0172, lines 5-8]	Pg. 42, lines 4-6
76.	(withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein detecting a change in fluorescence is by means of confocal microscopy or fluorescence correlation spectroscopy.	[0182]	Pg. 2, lines 1-2; pg. 50, lines 15-16 and pag. 51, lines 20-28

<p>77. (withdrawn and currently amended). A library of fluorescent ligands of formula I or I' or a kit comprising a compound thereof for use as claimed in claim 74 wherein the library or compound thereof comprises fluorescent ligand agonist(s) which maintains its binding affinity and functional activity or is an antagonist which maintains its binding affinity on linking or when linked to fluorescent moiety F'.</p>	<p>[0172, lines 1-5]</p>	<p>Pg. 42, lines 1-4</p>
<p>78. (withdrawn and currently amended). A kit comprising a library or a compound of formula I or I' as claimed in claim 47 or 64 and a target therefor provided as cell derived material selected from a cell line, expressing a GPCR, intracellular enzyme or drug transporter; membrane containing these proteins derived from such a cell line, solubilised receptor, enzyme or drug transporter or GPCR array from that cell line.</p>	<p>[0204, lines 1-5]</p>	<p>[0185, lines 3-6]</p>
<p>79. (withdrawn). Kit as claimed in Claim 78 wherein the cell derived material is provided in one of three forms: (1) from cells expressing a green fluorescent protein tagged receptor, intracellular enzyme or drug transporter; (2) from cells expressing an epitope tag for a commercially available fluorescent antibody or (3) a wild-type protein for which a specific fluorescent antibody is also provided.</p>	<p>[0204, lines 5-end]</p>	

80-82. (canceled).

83. (withdrawn and currently amended). Library as claimed in Claim 59-55 comprising a plurality of compounds of the formula

Lig₁-L₂-Fl

wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers

wherein Fl is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon Green™ and its derivatives including Texas-red™, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl chloride or its analogues or derivatives Cascade Blue™, Evoblu and fluorescent derivatives thereof, pyrenes and pyridoxazoles derivatives, the oxazine dyes, the dyes (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the AlexaFluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, erythrosin, eosin, pyrene, anthracenes, acridines, fluorescent phycoobiliproteins and their conjugates and fluoresceinated microbeads, Rhodamine and fluorescent derivatives thereof including Rhodamine Green™ including the tetraethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol Green™, coupled to amine groups using the isocyanate, succinimidyl ester or diisothiocyanate reactive groups,

and

wherein Lig-J₁, L-J₄ is selected from the formulae Lig-a, Lig-b, Lig-e and Lig-f wherein:

Lig-a comprises linking functionality J_L which is amine, and is of the formula, in either of the following forms given:

Lig-a¹



wherein

Ra⁴ comprises linking functionality J_L and J_T which is amine;

X¹ and X² are each O;

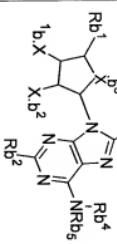
Ra³ is H;

each of Ra¹ and Ra² is n-propyl;

Ra⁴ is P⁻ substituted phenyl wherein the substituent is heteroalkyl amide amine; and includes L which is a single bond or is C₁₋₅₀ alkyl optionally substituted by C₁ alkyl and including

the formula $-(\text{CH}_2)_n$, where n is 3 to 8, optionally including one or more heteroatoms -O;

Lig.b comprises linking functionality J_L which is amine, and is



wherein
ring substituents X^{b1} and X^{b2} are each OH;

ring heteroatom X^{b3} is -O-;

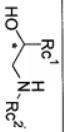
Rb¹ is CONHEt or CH₂OH;

and each of R^{b2} and R^{b3} is H;

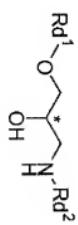
Rb⁴ is H;

Rb⁵ comprises linking functionality J_T which is amino, and linker L.b selected from saturated C₁-12 aliphatic and C₆-24 aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;

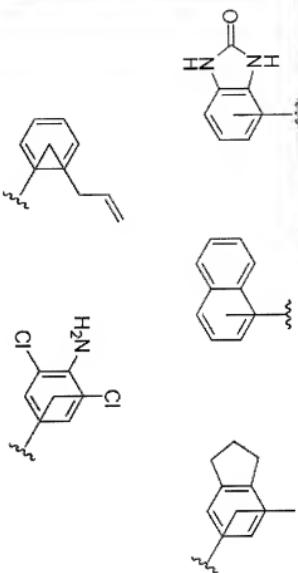
Lig.c comprises linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
 Rc^1 is m-, p- dihydroxyphenyl; and
 Rc^2 comprises linking functionality J_L which is amine, and linker L.c which is selected from C_1 - C_{12} straight chain alkyl, C_{6-12} cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C_1 aliphatic; or Lig_d comprises a linking functionality J_L which is amine and is



as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,
 Rd^1 is selected from the structures

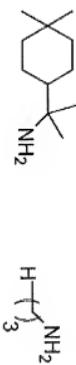


and a substituted C₁₋₂₀ spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

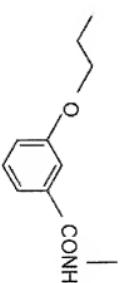
Rd² comprises linking functionality J_T which is amine, and linker L_d which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁₋₆ aliphatic; or Rd² is C₁₋₆ straight chain alkyl including ether O and substituted by C₆₋₁₀ aryl which is OH and oxo substituted and comprises linker L_d as hereinbefore defined.

84. (withdrawn). Library as claimed in claim 83 wherein

R.a⁴, R.b⁵ or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected from (CH₂)_m wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L. J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino methane or the structure



or R.d² comprises the following OH substituted aryl structure wherein linking functionality J_T is shown as amine, L.d is as hereinabove defined and includes J_T which is amine:



85. (canceled).

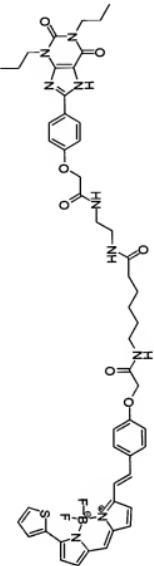
86. (withdrawn and currently amended). Library as claimed in Claim 83-47 wherein FI is selected from Texas Red TM, Cy5.5 or Cy5 or analogues thereof, DY-630, DY-640, DY-650 or DY-655 or analogues thereof, ATTO 655 or ATTO 680 or analogues thereof, EviBlue 30 or

Docket No. Q111431

[0117]

analogues thereof, Alexa 647 or analogues thereof, BODIPY 630/650 X and analogues thereof including BODIPY 630/650 X.

87. (withdrawn and currently amended). Library as claimed in claim 86 comprising a compound selected from the following structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers:



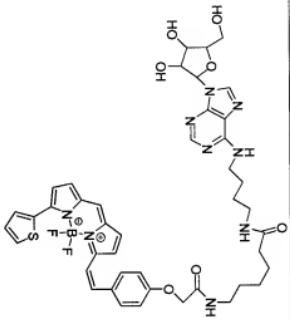
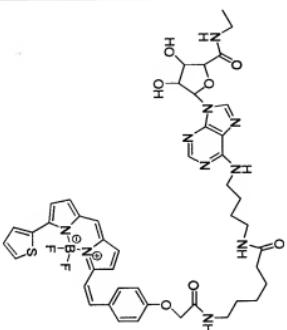
XAC-BODIPY 630/650 X

[0219]

Pg. 59, lines 1-3

Docket No. Q111431

ABA-BY620

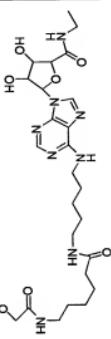


6

[0237]

Pg. 65, lines 1-3

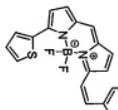
ABEA-BY630



[0239]

Pg. 66, lines 2-3

APEA-BY 630



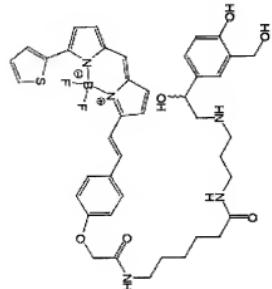
[0245]

Pg. 67, lines 1-3

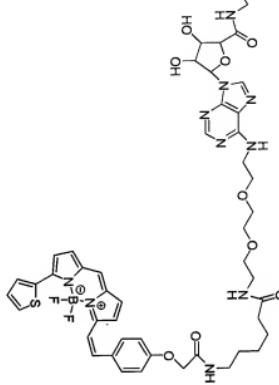
Docket No. Q111431

Docket No. Q111431

And



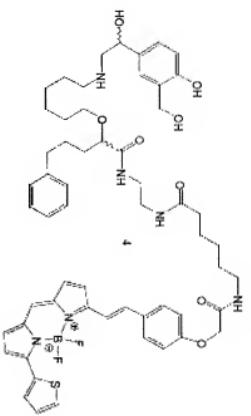
ABIPEA - BY630



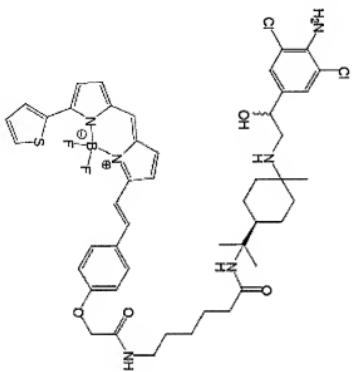
[0249]

[0249]
[0250]

Pg. 68; scheme
4 and pg. 68,
lines 1-3



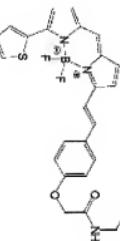
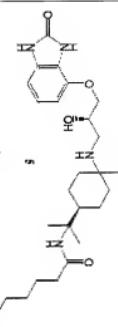
Salmeterol BY 630/650



[0251]

Pg. 59, lines 15-
20

Clenbuterol BY 630/650



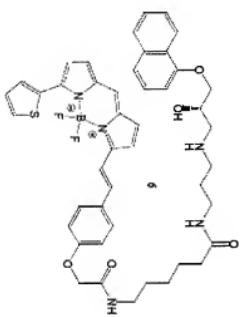
CGP12177-BY 630/650

[252]

Pg. 70, line 5

[252]

Pg. 70, line 5



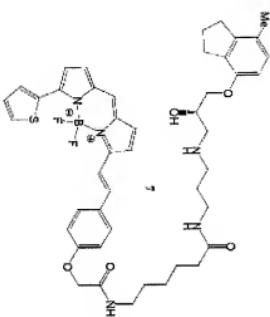
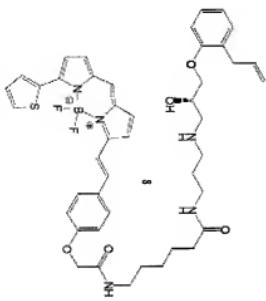
Propranolol BY630/650

[0252]

Pg. 70, line 10

Docket No. Q111431

ICI118551-BY630/650



[252]

Pg. 70, line 10

[0252]

Pg. 70, line 10

88. (currently amended). Compound as claimed in Claim 67 of the formula Light-Label wherein any optically-active fluorescent ligand is present as a racemate or as one of its optically	
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ACTIVE ISOMERS

wherein II is selected from wherein II is selected from dyes in particular including fluorescein, fluorescein derivatives including FITC, and fluorescein-like molecules including Oregon GreenTM and its derivatives, Texas RedTM, 7-nitrobenz-2-oxa-1,3-diazole (NBD) and derivatives thereof, coumarin and derivatives, naphthalene including derivatives of dansyl-chloride or its analogues or derivatives, —Cyaede—BlueTM, EviBlue— and —fluorescent derivatives thereof, Pyrenes— and pyridoxazole derivatives, the cyanine dyes, the dyes and (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the AlexaFluor dyes and derivatives, BDI dyes including the commercially available BodipyTM dyes, erythrosin, eosin, pyrenes, anthracones, acrilates, fluorescent phycoobiliproteins and their conjugates and fluoresceininated microbeads, Rhodamine and —fluorescent— derivatives — thereof — including — Rhodamine — GreenTM — including — the tetramethylrhodamines, X-rhodamines and Texas Red derivatives, and Rhodol GreenTM, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl reactive groups, and

wherein $\text{Lig}_1, \text{Lig}_2, \text{Lig}_3$ is selected from the formulae $\text{Lig}_a, \text{Lig}_b, \text{Lig}_c$ and Lig_d wherein:

Lig_a comprises linking functionality I_1 which is amine, and is of the formula, in either of the following forms given:

Lig_a^1



wherein

Ra⁴ comprises linking X¹ and X² are each O;

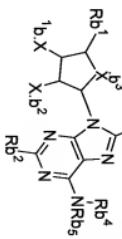
R.a³ is H;

each of R.a¹ and R.a² is n-propyl;

R.a⁴ is p- substituted phenyl wherein the substituent is heteroalkyl amide amine; and

the formula $-(CH_2)_n$, where n is 3 to 8, optionally including one or more heteroatoms $-O-$;

Lig.b comprises linking functionality J_L which is amine, and is

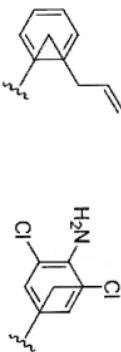
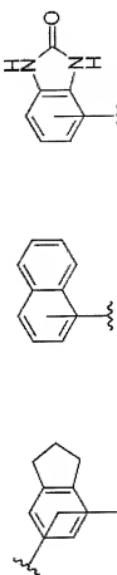


wherein ring substituents $X.b^1$ and $X.b^2$ are each OH; ring heteroatom $X.b^3$ is -O-;

<p>Rb¹ is CONHET or CH₂OH; and each of R.b² and R.b³ is H; Rb⁴ is H; Rb⁵ comprises linking functionality J_T which is amino, and linker L.b selected from saturated C₁₋₁₂ aliphatic and C₆₋₂₄ aromatic, optionally substituted by one or more C₁ alkyl and optionally including one or more heteroatoms O or cyclic groups;</p> <p>Lig.c comprises linking functionality J_L which is amine and is</p> $\text{HO} \cdot \text{N}(\text{Rc}^1) \text{Rc}^2$ <p>as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,</p> <p>Rc¹ is m-, p- dihydroxyphenyl; and</p> <p>Rc² comprises linking functionality J_T which is amine, and linker L.c which is selected from C₁₋₁₂ straight chain alkyl, C₆₋₁₂ cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic;</p> <p>or Lig.d comprises a linking functionality J_L which is amine and is</p> $\text{Rd}^1 \text{O} \sim \text{*} \sim \text{N}(\text{Rd}^2) \text{H}$	
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as a racemate or as one of its optically active isomers wherein * indicates an optically active centre,

Rd¹ is selected from the structures

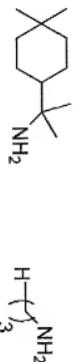


and a substituted C₁-20 spiro aromatic ring system comprising a single aromatic ring and a heteroaryl and optionally halo substituted; and

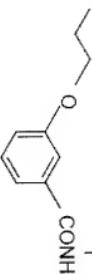
Rd² comprises linking functionality J_r which is amine, and linker L_d which is selected from C₁-12 straight chain alkyl, C₆-12 cycloalkyl or aryl and combinations thereof optionally comprising one or more heteroatoms O and optionally substituted by C₁ aliphatic; or Rd² is C₁-6 straight chain alkyl including ether O and substituted by C₆-10 aryl which is OH and oxo substituted and

comprises linker L.d as hereinbefore defined, with the proviso that the compound is not a compound excluded in Claim 18.

89. (currently amended). Compound as claimed in Claim 88 wherein R.a⁴, R.b⁵ or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.a, L.b, L.c or L.d selected from (CH₂)_m wherein m is 3, 4, 6 or 8 or is in the range 3 to 8 or 2 to 12 optionally including one or more substituents C₁, or J_L L.J_T is mono or polyethylene glycol diamine, or L.a is a single bond; or R.c² or R.d² comprises linking functionality J_T which is amino, and linker L.c or L.d selected from C(CH₃)₂CH₂Ph and mono amino methane or the structure



or R.d² comprises the following OH substituted aryl structure wherein linking functionality J_L is shown as amine, J_d is as hereinabove defined and includes J_T which is amine:



with the proviso that when \mathbb{L}^{42} -Lig is XAC ie in Lig a when each of Ra¹ and Ra² is propyl, Ra³ is H and Ra⁴ is -Ph-OCH₂CONH(CH₂)₂NH⁻, and L is a single bond Fl is not BODIPYTM 630/650 X, or
b) when Lig is ABEA, ie n is 4 and L is a single bond Fl is not BODIPYTM 630/650 X.

90. (canceled)

91. (currently amended). Compound as claimed in Claim 88-64 wherein Fl is selected from Texas RedTM Cy5.5 or Cy5, or analogues thereof, DY-630, DY-640, DY-650 or DY-655 or analogues thereof, ATTO 655 or ATTO 680 or analogues thereof, EvioBlue 30 or analogues thereof, Alexa 647 or analogues thereof, BODIPY 630/650-X and analogues thereof including BODIPY 630/650-X.

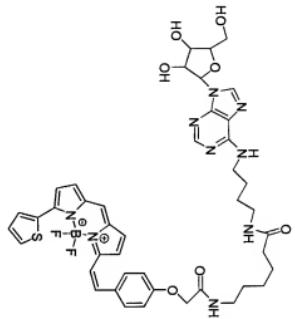
[0117]

92. (withdrawn and currently amended). Compound selected from the structures wherein any optically active fluorescent ligand is present as a racemate or as one of its optically active isomers;

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ABA-BY630

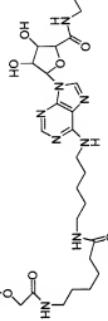


[0225]

Pg. 57, lines 1-3

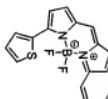
[0239]

Pg. 59, lines 1-3

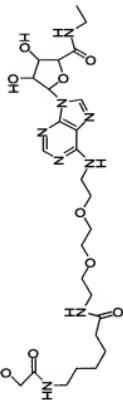


[0245]

Pg. 67, lines 1-3

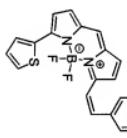


APEA-BY 630



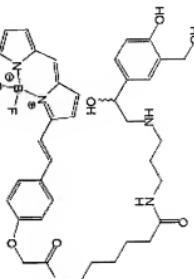
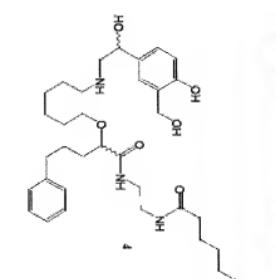
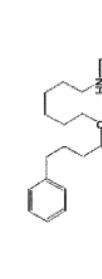
[0249]

Pg. 68, scheme
4

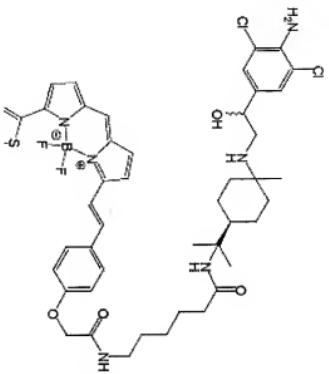


ABPEA - BY630

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<p>[0249] [0250]</p>	<p>Pg. 68; scheme 4 and pg. 69, lines 1-3</p>	
<p>[251]</p>	<p>Pg. 69, lines 15- 20</p>	
<p>[0252]</p>	<p>Pg. 70, line 5</p>	

Salmeterol BY 630/650



[0252]

Pg. 70, line 5

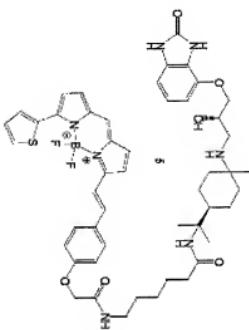
[0252]

Pg. 70, line 10

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Clenbuterol BY 630/650

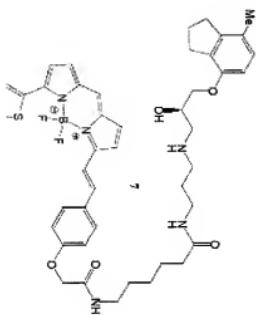
[0252]



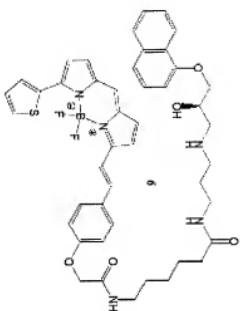
CGP12177-BY 630/650

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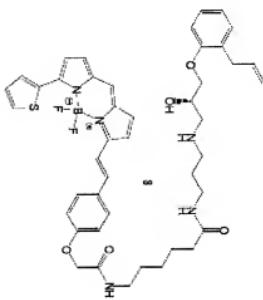
Docket No. Q111431



Propranolol BY630/650



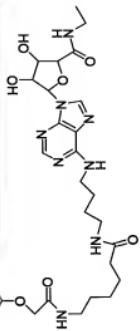
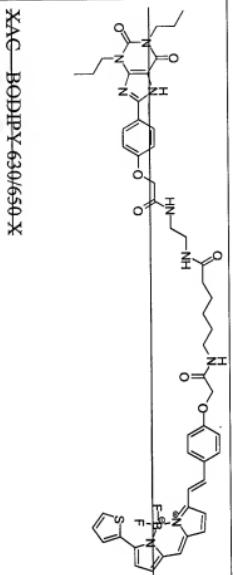
ICII18551-BY630/650



Alprenolol-BY630/650

and optionally additionally:

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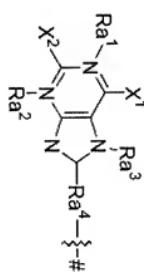


ABEΛ-BY660.

Docket No. Q111431

93. (new and withdrawn). Library of tagged non-peptide ligands comprising moiety Lig and I selected from formula Lig-a-I..a - Lig-e..e associated with a Tag which is an entity -Fl wherein the or each -Fl is selected from a red, near ir or blue dye and wherein: Lig-a- is suitably of the formulae, in either of the following forms given:

Liga¹ -



Wherein X¹ and X² are each independently selected from H, =O, OR.a, NR.a, NHR.a;

X¹ and X² are each preferably =O;
 each of Ra, Ra¹, Ra² and Ra³ independently is selected from H or C₁₋₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl optionally mono or multi hydroxy or halo substituted, such as CH₃OH, CH₂F or CH₂CHOHCH₂OH;

[0060] [0115]

Pg. 16, line 16

Pg. 27, line 27

(continuous)

[0061]

[0063]

Pg. 27, line 27

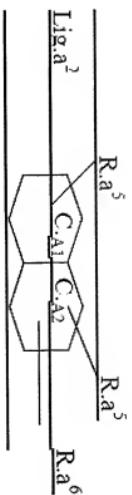
[0066]

R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

[0067]

preferably R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone, (di)amine, (di)amide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc, for example is cyclohexyl, cyclopentyl, ethoxy, (CH₂)₂PhPh, CH₂Ph, CONH(CH₂)_nCONH, CH₂CONH(CH₂)₂NH, CH₂PiNHCOCH₂, CH₂CH₂OOCOCH₂, succinimidyl ester, NHCOCH₂, CH₂(CH₃)NCOCH₂, H₂N(CH₂)_nNHCOCH₂, H₂NNHCOCH₂CH₂CONH(CH₂)₂NHCOCH₂, HOPhCH₂N(CH₂CH₃HOAc)(CH₂)₂NHCOCH₂, heterocyclic-(CH₂)_nCONH(CH₂)_pNHCOCH₂, heterocyclic-NHCON(heterocyclic)COCH₂ and the like;

or Lig.a² is of the formula Lig.a²-



[0069]

[0070]
[0071]

wherein each of C.A1 and C.A2 is independently selected from aryl, heteroaryl, cycloalkyl and

heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -

C=C- group;

Each of up to seven R.a⁵ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH, hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)₂hex,

[0072]

[0073]

N(CH2CH2OH)2, c-hex, COOCH2CH3, CH2CH3;
or
any two or more of R.a⁵ form a one, two or three ring fused cyclic structure, preferably
comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms
common with the fused bicyclic Lig.a² structure;

and R.a⁶ is a moiety as defined for R.a⁵ above;

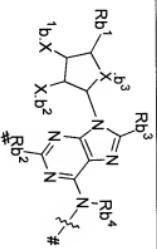
and -L.a- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as
hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as
a peptide or polypeptide for example gly or gly3, alkyl of formula -(CH₂)_n where n is 3 to 8,
preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -
O- or -S- or -CH=CH- and the like:

Lig.b is suitably of the formula Lig.b

Lig.b

[0075]

[0076]
[0077]



[0078]

wherein ring substituents X.b¹ and X.b² are independently selected from hydrocarbon such as alkyl or SR_x, NR_x and OR_x wherein (each) R_x is selected from H, C₁-alkyl, alkenyl;

ring heteroatom X.b³ is selected from -S-, -O- and -CH₂;
 Rb¹ is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₄ aliphatic, or C₁₋₃ alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine; preferably R.b¹ comprises a carbonyl substituted by H, alkyl or a linear or cyclic primary, secondary or tertiary amine, substituted C₁₋₃ alkyl, cycloalkyl or amide, more preferably cyclopropyl, or CONHC₁₋₃alkyl such as CONHET or

CH₂OH

and each of R.b² and R.b³ is selected from H, halo, hydroxy, thiol, amine, COOH,

CHO, hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C₁₋

²⁰ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or

[0079]
 [0082]

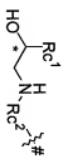
alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

Rb^4
is H;

-L,b- is hereinbefore defined for -L-, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L,I- or -L,II- as hereinbefore defined, most preferably is -(CH₂)_m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -(Ph-CH₂CONH₂-(CH₂)₂;

Lig,c is suitably a non-peptide of the formula

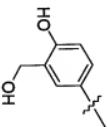
Lig,c HO-C*(R,c¹)-CH₂NH-R,c²-



Where * indicates an optically active centre and

Wherein R,c¹ is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O,

optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH, phenyl, m,p-dihydroxy phenol or m,m-dihydroxyphenol, m,m-diCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as



[0087]

R.c² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

[0088]

Preferably R.c² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic optionally substituted by OH and optionally including heteroatoms selected from

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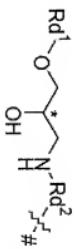
[0086]

N₂O, preferably including an ether O, such as selected from -(CH₂)₆OCH((CH₂)₃Ph), CHCH₃(CH₂)₂Ph, CHCH₃CH₂PhOH, C(CH₃)₂CH₂;

-L-c- is as hereinbefore defined for -L- and is suitably of formula -L-I- or -L-II- as hereinbefore defined, more preferably is selected from C₁₋₁₂ alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula

Lig.d R.d¹OCH₂C*HOHCH₂NH-R.d²#



[0091]

[0090]

Where * indicates an optically active centre and where # indicates the site of linking to the fluorescent tagging moiety

Wherein

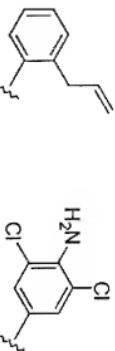
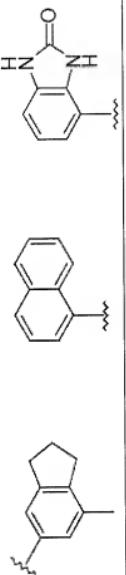
R.d¹ is saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional

substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

Preferably R_d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R_d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaryl or heterocycloaryl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

[0093]

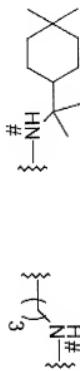
[0094]



R,d²

is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁-12 branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any C₁-12 aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C₁-6 branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆-10 aryl, for example of the formula:

[0096]



i.pr, i.bu, $\text{CH}_2\text{CH}_2\text{O}$ (m-CONH₂, p-OH) phenol, $\text{CH}_2\text{CH}_2\text{O}$ (o-OCH₃) phenol

-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;

Lige

comprises a cell permeant moiety or is associated with a cell permeant L or F1 moiety and is suitably of the formula , in either of the following forms given:

[0097]
[0098]

[0099]

[0100]

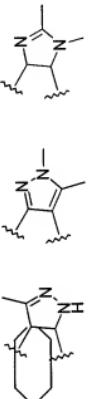
Lige¹



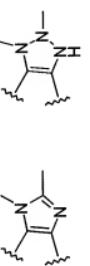
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wherein

h is selected from



[0102]



[0103]



[0104]

each optionally substituted by $R.e^3 - R.e^4$ wherein $R.e^1 - R.e^4$ are as $R.a^1 - R.a^4$ defined above or in which $R.e^3$ is C_5 -linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg

ortho-OEt, meta-SO₂N

NCH₃

each X is independently selected from H, =O, -OR⁵, =N, HN, NR⁶, HR⁶, and

[0106]

aryl optionally substituted by ether, or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-OCH₂CH₂CH₃;

and

where R.e⁵ is as defined above for R.e¹ above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;

R.e⁶ is as defined above for R.e¹ above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C₅₋₈ alkyl such as methyl, piperazinyl, sulphonyl and the like;

or Lig^e is of the formula Lig.e²

Lig.e²

(h) 5.6(h)

[0110]

[0109]

[0107]
[0108]

Wherein each of C_{E1} and C_{E2} is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring – C=C- group;

Each of up to seven $R.e^{11}$ is a substituent of a ring carbon or a ring heteroatom and: is independently selected from saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C_{1-12} aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxyl, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as $=O$, OCH_3 , $CH_2Ph(OCH_3)_2$, $O(CH_2)_3CON(CH_3)_2$ hex, $N(CH_2CH_2OH)_2$ hex, $COOCH_2CH_3$, CH_2CH_3 , or any two or more of $R.e^{11}$ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic $L.e^3$ structure; and $R.e^{12}$ is a moiety as defined for $R.e^{11}$ above;

Preferably $L.e^1$ is of the formula $L.e^1$ as hereinbefore defined in particular where $R.e^2$ and $R.e^3$ are respectively propyl and butyl; $-L.e-$ is suitably as hereinbefore defined for $-L.a-$.

94. (new and withdrawn). Library as claimed in claim 93 wherein the or each F_i is selected

[0115]

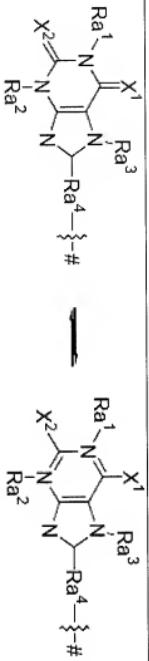
from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridyloxazole derivatives, the cyanine dyes, the dyes (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.

95. (new): Compound which is a tagged non-peptide ligand comprising moiety Lig and L selected from formula Lig-a-L-a- -Lig-e-L-e associated with a Tag which is an entity -Fl wherein -Fl is selected from a red, near ir or blue dye and wherein:

Lig-a- is suitably of the formula, in either of the following forms given:

Liga¹-

[0063]	
[0064]	



[0065]

Wherein

X¹ and X² are each independently selected from H, =O, OR.a, NR.a, NHR.a; X¹ and X² are each preferably =O;

each of Ra, Ra¹, Ra² and Ra³ independently is selected from H or C₁₋₁₄ linear or branched alkyl, preferably H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl or isobutyl, optionally mono or multi hydroxy or halo substituted, such as CH₂OH, CH₂F or CH₂CHOHCH₂OH;

R.a⁴ is selected from a heteroatom O, S or substituted or unsubstituted amine or

saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

preferably R.a⁴ is selected from optionally substituted aryl, cycloalkyl, alkyl, ketone,

(diamine, (dijamide, more preferably optionally substituted alkoxy, cycloalkyl, amine, amide, carboxylic acid or optionally o-, m- or p- substituted phenyl wherein

[0066]

substituents include aryl, alkyl, cycloalkyl, heteroaryl or heteroalkyl, amine, amide, carboxyl, carbonyl etc. for example is cyclohexyl, cyclopentyl, ethoxy, $(\text{CH}_2)_2\text{PhPh}$, CH_2Ph , $\text{CONH}(\text{CH}_2)_n\text{CONH}$, $\text{CH}_2\text{CONH}(\text{CH}_2)_2\text{NH}_2$, $\text{CH}_2\text{PhNHCOCH}_2$, $\text{CH}_2\text{CH}_2\text{OCOCH}_2$, succinimidyl ester, NHCOCOCH_2 , $\text{CH}_2(\text{CH}_3)\text{NCOCH}_2$, $\text{H}_2\text{N}(\text{CH}_2)_2\text{NHCOCH}_2$, $\text{H}_2\text{NNHCOCOCH}_2$, $\text{HOPhCH}_2\text{N}(\text{CH}_2\text{CH}_3\text{HOAc})(\text{CH}_2)_2\text{NHCOCH}_2$, heterocyclic- $(\text{CH}_2)_4\text{CONH}(\text{CH}_2)_2\text{NHCOCH}_2$, heterocyclic- $\text{NHCCON}(\text{heterocyclic})\text{COCH}_2$, and the like;

or Lig. a- is of the formula Lig. a^2



[0069]
[0070]
[0071]

wherein each of $\text{C}_{\text{A}1}$ and $\text{C}_{\text{A}2}$ is independently selected from aryl, heteroaryl, cycloalkyl and

heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -

$\text{C}=\text{C}$ -group;

Each of up to seven R.a^5 is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from H, halo, hydroxy, thiol, amine, COOH , hydrazine, cyano, saturated or unsaturated, substituted or unsubstituted $\text{C}_{\text{1-20}}$ branched or straight chain

aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₂CON(CH₃)₂hex, N(CH₂CH₂OH)₂, c. hex, COOCH₂CH₃, CH₂CH₃;

or any two or more of R_a⁵ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl, 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig_a² structure;

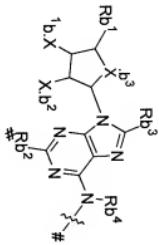
and R_a⁶ is a moiety as defined for R_a⁵ above;

and -L_{a-} is as hereinbefore defined for -L- and is suitably of formula -I-I- or -I-II- as hereinbefore defined, more preferably is selected from a single bond, amino acid or amide such as a peptide or polypeptide for example gly or gly₃, alkyl of formula -(CH₂)_n where n is 3 to 8, preferably 3, 4 or 6, optionally including one or more heteroatoms or unsaturated groups, such as -O- or -S- or -CH=CH- and the like:

Lig_b is suitably of the formula Lig_b

Lig_b

[0073]



[0075]

wherein ring substituents $X.b^1$ and $X.b^2$ are independently selected from hydrocarbon such as alkyl or SR_x , NR_x and OR_x wherein (each) R_x is selected from H, C_{1-5} alkyl, alkenyl;

ring heteroatom $X.b^3$ is selected from -S-, -O- and $-CH_2-$;

Rb^1 is selected from saturated or unsaturated, substituted or unsubstituted C_{1-4} aliphatic,

or C_{1-3} alicyclic optionally including one or more heteroatoms N, O, S, P, wherein substituent(s) are selected from one or more cycloalkyl, heterocyclic, hydroxy, oxo, halo, amine, preferably Rb^1 comprises a carbonyl substituted by H, alkyl or a linear

or cyclic primary, secondary or tertiary amine, substituted C_{1-3} alkyl, cycloalkyl or amide, more preferably cyclopropyl, or $CONHC_{1-3}$ alkyl such as CONHET or

CH_2OH

and each of $R.b^2$ and $R.b^3$ is selected from H, halo, hydroxy, thiol, amine, $COOH$,

CHO , hydrazine, cyano or saturated or unsaturated, substituted or unsubstituted C_{1-2} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof,

any of which may comprise one or more heteroatoms selected from N, O, S, P;

[0076]

wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, preferably from H, halo or hydroxy, preferably H or Cl;

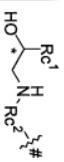
Rb⁴

is H;

-L.b- is as hereinbefore defined for -L, more preferably saturated and unsaturated substituted or unsubstituted C₁₋₁₂ aliphatic or C₁₋₂₄ aromatic as defined for -L- preferably including one or more heteroatoms O, S or N, cyclic or heterocyclic groups, more preferably is of formula -L.I- or -L.II- as hereinbefore defined, most preferably is -CH₂)m wherein m is 2 to 12, preferably 3, 4, 6 or 8, or is -CPh-CH₂CONH₂ (CH₂)₂-;

Lig c is suitably a non-peptide of the formula

Lig c HOCl*(R.c¹)CH₂NH-R.c².

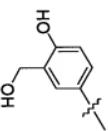


Where * indicates an optically active centre and

[0079]

[0082]

Wherein R_{c1} is C₆₋₁₄ aryl optionally including one or more heteroatoms selected from H, O, optionally substituted by OH, Hal eg Cl, NH₂, NHC₁₋₃alkyl, sulphonamide, oxoamine (-CONH₂) and the like, more preferably mono, di or tri substituted phenyl or quinoline wherein substituents include OH, Cl or NH₂, more preferably m-CH₂OH, p-OH phenyl, m-,p-dihydroxy phenol or m-,m-dihydroxyphenol, m,m-dCl, p-NH₂ phenol, p-OH, m-CONH₂ phenol or 5-OH, 8-quinoline and the like, such as



R_{c2}² is selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀, preferably C₁₋₁₂, branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P, wherein optional substituents are selected from any optionally substituted C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like and combinations thereof;

[0086]

Preferably

R_{c2}² is selected from C₁₋₆ branched or straight chain aliphatic, C₆₋₁₀ araliphatic

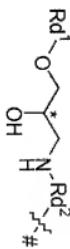
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optionally substituted by OH and optionally including heteroatoms selected from N, O, preferably including an ether O, such as selected from $-(CH_2)_6OCH(CH_2)_3Ph$, $CHCH_2(CH_2)_2Ph$, $CHCH_2CH_2PhOH$, $C(CH_3)_2CH_2$; [0087]

-L.c- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is selected from C_{1-12} alkyl, amide etc;

Lig.d is suitably a non-peptide of the formula

Lig.d $R.d^1OCH_2C^*HOHCH_2NH-R.d^2\#$



Where * indicates an optically active centre and where # indicates the site of linking to the fluorescent tagging moiety

[0090]

Wherein $R.d^1$ is saturated or unsaturated, substituted or unsubstituted C_{1-20} branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional

[0088]

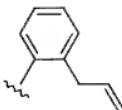
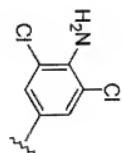
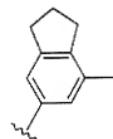
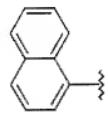
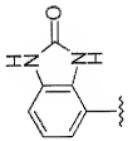
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substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like;

Preferably R_d¹ is substituted or unsubstituted C₁₋₂₄ aralkyl or heteroaralkyl, including single ring and fused ring systems with (hetero)aryl or cycloalkyl rings, wherein optional substituents include C₁₋₆ alkyl, alkoxy, ether, carbonyl, alkenyl, amine, amide each optionally carbonyl, amide, halo or OH substituted, or halo such as chloro or OH, preferably R_d¹ is unsubstituted or substituted alkyl, alkenyl, halo, amine, amide, carbonyl, ketone, ether substituted phenyl or naphthyl, illustrated as follows, most preferably mono-, di-, tri- or tetra substituted mono or polycyclic fused aryl or cycloaroyl or heterocycloaroyl such as phenyl, carbazole or structures shown below or spiro ring systems, most preferably mono-, di-, tri- or tetra alkoxyalkyl, alkoxyalkoxyalkyl or CF₃ substituted phenyl or unsubstituted or monosubstituted naphthalene or 5,6 ring systems most preferably of the structures:

[0092]

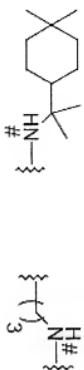
[0093]



[0094]

R.d²

is substituted or unsubstituted amine, saturated or unsaturated, substituted or unsubstituted C₁₋₁₂ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of which may comprise one or more heteroatoms selected from N, O, S, P; wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, more preferably amine, C₁₋₆ branched or straight chain alkyl optionally including ether O, and optionally substituted by C₆₋₁₀ aryl, for example of the formula:



[0096]

i.pr, i.bu, CH₂CH₂O (m-CONH₂, p-OH) phenol, CH₂CH₂O (o-OCH₃) phenol

-L.d- is as hereinbefore defined for -L- and is suitably of formula -L.I- or -L.II- as hereinbefore defined, more preferably is a single bond or is as hereinbefore defined for -L.a-;

Lige¹ comprises a cell permeant moiety or is associated with a cell permeant L or

F1 moiety and is suitably of the formula , in either of the following forms given:

[0097]

[0098]

[0099]

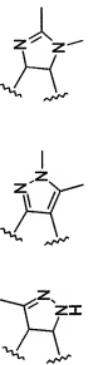
Lige¹



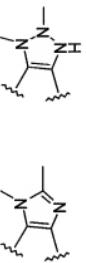
[0100]

wherein

h is selected from



[0102]



[0103]

each optionally substituted by $R.e^3 - R.e^4$ wherein $R.e^1 - R.e^4$ are as $R.a^1 - R.a^4$ defined above or in which $R.e^3$ is C_5 -linear or branched alkyl, optionally mono or multi hydroxy or halo substituted or is aryl optionally substituted by alkoxy, sulfonyl and the like eg

[0104]

ortho-OEt, meta-SO₂N

NCH₃

each X is independently selected from H, =O, -OR^e, =N, HN, NR^e, HR^e, and aryl optionally substituted by ether; or X is aryl optionally alkyl or alkoxy substituted such as Ph-ortho-OCH₂CH₂CH₃;

and where R^e is as defined above for R^d above or forms a fused cyclic ring together with the adjacent ring N atom; preferably 1 or 2 fused 5 membered cyclic rings;

and R^e is as defined above for R^d above or is selected from optionally substituted phenyl wherein optional substituents include ether such as o-ethoxy or o-propoxy, alkyl, OH and the like, sulphonyl, carbonyl and the like substituted by heterocyclic, or cyclic C₅₋₈ alkyl such as methyl, piperazinyl, sulphonyl and the like;

or Lig^e is of the formula Lig^e²

Lig^e²
(b) 5,6(h)

Wherein each spiro ring optionally comprises zero or one or more heteroatoms h which are preferably N, more preferably (b) comprises zero or

1 N heteroatom and

5,6(h) comprises zero, 1 or 2 N

heteroatoms and is unsaturated or comprises one or two -C=C- or -C=N- groups; and wherein each ring is optionally substituted by one or more oxo, CO, COOH, C₁₋₆ alkyl or linear or cyclic alkoxy such as methoxy, ethoxy or cyclopentenyl oxy optionally substituted by one or more oxo, CO, COOH, CN, or C₁₋₆ alicyclic or amine groups, amine or one or more spiro or fused heterocycles;

or Lig.e is of the formula Lig.e³

R.e¹¹

R.e¹¹

Lig.e³

C.E1

C.E2

R.e¹²

Wherein each of C.E1 and C.E2 is independently selected from aryl, heteroaryl, cycloalkyl and heterocyclic, more preferably from phenyl, or aryl containing 1 or 2 ring heteroatoms, or heterocyclic containing 1 ring heteroatom and/or 1 ring -C=C- group;

Each of up to seven R.e¹¹ is a substituent of a ring carbon or a ring heteroatom and:

is independently selected from saturated or unsaturated, substituted or unsubstituted C₁₋₂₀ branched or straight chain aliphatic, aromatic, alicyclic and combinations thereof, any of

which may comprise one or more heteroatoms selected from N, O, S, P, and wherein optional substituents are selected from any C₁₋₁₂ aliphatic, aromatic or alicyclic substituents any of which may comprise one or more heteroatoms as hereinbefore defined, hydroxy, thiol, halo, amine, hydrazine, oxo, cyano, and the like, such as =O, OCH₃, CH₂Ph(OCH₃)₂, O(CH₂)₃CON(CH₃)₂, hex, N(CH₂CH₂OH)₂, c. hex, COOCH₂CH₃, CH₂CH₃;

or any two or more of R.e¹¹ form a one, two or three ring fused cyclic structure, preferably comprising a fused 3 ring aryl 5-heterocyclic, 6-heterocyclic structure having 4 ring atoms common with the fused bicyclic Lig.e³ structure;

and R.e¹² is a moiety as defined for R.e¹¹ above;

Preferably Lig.e is of the formula Lig.e¹ as hereinbefore defined in particular where R.e² and R.e³ are respectively propyl and butyl;

-L.e- is suitably as hereinbefore defined for -L.a-.

96. (new). Compound as claimed in claim 95 wherein F1 is selected from the following dyes: Texas red™, coumarin and derivatives, Cascade Blue™, EvoBlue and fluorescent derivatives thereof, pyrenes and pyridoloxazole derivatives, the cyanine dyes, the dyomics (DY dyes and ATTO dyes) and fluorescent derivatives thereof, the Alexafluor dyes and derivatives, BDI dyes

[0115]

	including the commercially available Bodipy™ dyes, pyrenes, anthracenes, acridines, fluorescent phycobiliproteins and their conjugates and fluoresceinated microbeads, and Texas Red derivatives, coupled to amine groups using the isocyanate, succinimidyl ester or dichlorotriazinyl-reactive groups.	
97	(new and withdrawn) Process for the preparation of a library as claimed in Claim 59, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.	[0134]
98	(new and withdrawn) Process for the preparation of a compound as claimed in Claim 60, wherein reactive groups Y_{Lig} , Y_L , Y_T have suitable reactive group functionalities for linking by addition or addition – elimination reaction.	[0134]